Environmental Health Perspectives Supplements
Vol. 102 Suppl 1:131-133 1994

A New Model of Shouldered Survival Curves

by Shigeru Kumazawa

Recently, the linear-quadratic equation has been used to construct the dose–response relationships of ionizing radiation. The radiobiological theory on which this relationship is based indicates that at low doses, the risk of a biological lesion being formed should depend linearly on dose if a single event is required or quadratically on dose if two events are required. The same approach has also been used to construct the shouldered survival curves, which indicate a lower response of cell killing at low doses of low linear energy transfer (LET) radiation than at high doses because of repair. However, a different approach is possible, derived from the concept of generating the hybrid lognormal distribution, in which the hybrid form of linear and logarithmic components of a random variable is used. The hybrid form is a formulation of the phenomenon in which there is a feedback mechanism against the large change in the random variable. This paper presents a new model of shouldered survival curves, called a hybrid scale model, which has two parameters: the inactivation constant and the protective factor. In the model, the surviving fraction, normalized by a protective factor plotted in a hybrid scale, is assumed to be linear against the dose. This simple model povides an implication of the shoulder of survival curve and the effect of recovery time of radiation damage, as well as giving a good to the well-known data of split-dose experiments with mammalian cells.

Introduction

Typical survival curves of exposed mammalian cells may have a steep slope of a semilogarithmic plot for densely ionizing radiation, but for sparsely ionizing radiation they usually have a small slope at low doses, followed by a curved shoulder leading to a substantially steeper slope at higher doses. A shouldered dose response indicates a lower effectiveness of cell killing at low doses of low linear energy transfer (LET) radiation than at high doses because some of the radiation damage has been repaired. This repair was demonstrated by Elkind and Sutton (*1*) in experiments with Chinese hamster cells irradated with two or more doses of X-rays separated by intervals of time.

The shouldered survival curves, $S(D)$, are usually described as a function of dose, D, by various models as follows: *a*) the single-target plus multitarget single-hit type

$$S(D) = exp(-D/_1D_0)[1 - \{1 - exp(-D/_nD_0)\}^n] \quad (1)$$

where $_1D_0$ is the inverse of the slope of the initial slope of the curve and $_nD_0$ is the inverse of the sensitivity of each of the n targets, and *b*) The linear-quadratic form

$$S(D) = exp\{-(\alpha D + \beta D^2)\} \quad (2)$$

where α and β are, respectively, the linear and the quadratic coefficient. Equation 2 may be generalized as a polynomial form of D.

The report of the United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR (*2*)] states that the initial slope, $exp(-D/_1D_0)$ in Equation 1 and α in Equation 2 is still a matter of debate, but this question is immaterial in the dose–response models of radiation-induced cancer, as both functions satisfactorily describe the experimental data for surviving fractions between 1.0 and 0.1.

In contrast to models based on the target theory, Hug and Kellerer (*3*) derived a different form of surviving fraction, $S(D)$, based on a concept of reactivity, $R(D)$, for the slope of the survival curve and compensational capability, $K(D)$, for reducing the reactivity as follows:

$$S(D) = exp[-R'D + (K_0/\gamma)\{1 - exp(-\gamma D)\}] \quad (3)$$

where R' is the final value of $R(D)$ when the compensational capability diminishes, K_0 is the initial compensational capability before irradation, and $K = K_0exp(-\gamma D)$ and $R(D) = R' - K_0exp(-\gamma D)$. This model was reported to fit the data of Elkind and Sutton (*1*) well.

This paper presents another possibility of the model building, extended from the concept of generating the hybrid lognormal distribution, which is defined as $\ln\rho X+\rho X \sim N(\mu,\sigma^2)$, $0 < x < \infty, \rho > 0$ (*4*). The hybrid form of linear and logarithmic terms of the random variable is a formulation of the phenomenon in which a feedback mechanism constrains the larger variation in the range of large values. Then we can expect that there might be a feedbck mechanism in biological systems that mitigates the large decrease of surviving fraction incurred by the given dose because of repair.

Department of Health Physics, Japan Atomic Energy Research Institute, Tokai-Mura, Ibaraki-Ken, 319-11, Japan.

This paper was presented at the International Biostatistics Conference on the Study of Toxicology that was held May 13–25, 1991, in Tokyo, Japan.

Proposal: A Hybrid Scale Model

Suppose that the surviving fraction, $s(D)$, is given as follows:

$$\ln(\rho S) + \rho S = a + bD, \quad (\rho > 0,\ b < 0). \tag{4}$$

For $D=0$, $S=1$, $a=\ln\rho+\rho$ or

$$\ln S - \rho(1 - S) = bD. \tag{5}$$

If we differentiate Equation 5 with respect to D and solve it with respect to dS/dD, *then*

$$dS/dD = bS/(1 + \rho S). \tag{6}$$

The same equation also results from differentiating Equation 4 with respect to D.

Equation 6 may be interpreted as the slope, dS/dD, of the survival curve on linear–linear coordinates, reduced by decreasing the absolute value of b in the reciprocal of $(1 + \rho S)$ via the negative feedback mechanism of dS/dD with the feedback parameter of ρ because of repair. Putting the simultaneous equations of the feedback mechanism, $dS/dD=b'S$ and $b'=b-\rho dS/dD$, and removing b', we get Equation 6.

If the slope of survival curve on linear–linear coordinates is $dS/dD=bS$, the surviving fraction is $S(D)=exp(bD)$ or $\ln S(D)=bD$, $b<0$, where b is the inactivation constant. Then the differentiation can be written as $d\ln(S)/dD=b$, which means that the slope of the survival curve on the semilog plot is constant. Defining the hybrid scale as $y=\text{hyb}(t)=\ln(t)+t$ in much the same manner as the log scale defined by $y=\ln(t)$, we can write the differentiation of Equation 6 as $d\,\text{hyb}(\rho S)/dD=b$, which means that the slope of the survival curve on the semihybrid (a hybrid scale of surviving fraction) plot is constant. Thus the shoulder of survival curve disappears if we plot the data on semihybrid paper by introducing a protective factor, ρ.

Application of Model

There is much survival data concerning established cells exposed to ionizing radiation. Data suitable to test the model come from split-dose experiments with V79-1 cells after 2.5 and 23 hr of incubation at 73°C following a first dose of 5.05 Gy (*1*). Hug and Kellerer (*3*) also used the same data to test their model of Equation 3 shown above. However, the data must be obtained by reading the plots of Figure 11 of Elkind and Sutton (*1*). Table 1 shows these data. The given data are a set of (D_i,S_i), $(i=1 \text{ to } n)$, where D_i is the ith dose, and S_i is the surviving fraction of cells exposed to that dose. Dividing Equation 5 by the killing fraction, 1-S, we have

$$\frac{\ln S}{1 - S} = \rho + \frac{D}{1 - S}b \tag{7}$$

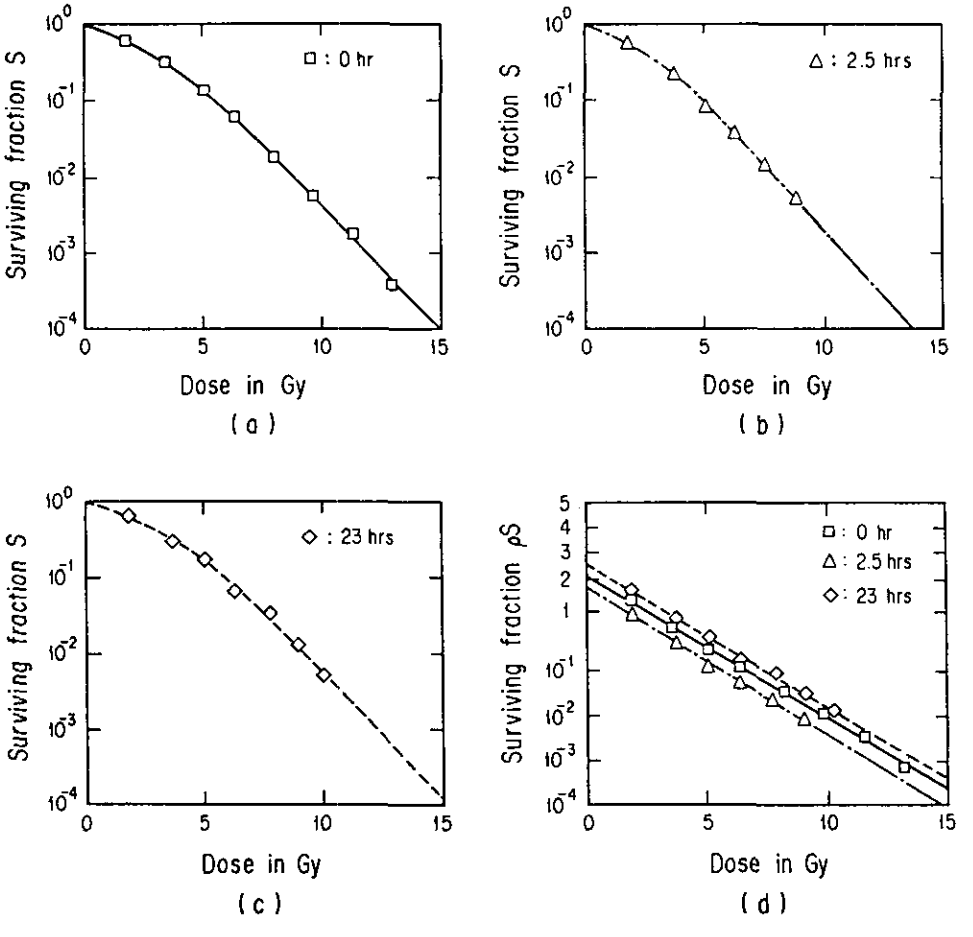

FIGURE 1. Results of fitting the hybrid scale model to survival data of irradiated mammalian cells (*1*) with different incubation times.

Putting $x_i=D_i/(1-S_i)$, $y_i=\ln S_i)$, $b_0=\rho$ and $b_1=b$, we have the linear model.

$$y_i = b_0 + b_1 x_i + \varepsilon_i, \quad (8)$$

where ϵ_i is an error term. Equation 8 was used for both the hybrid scale model and the linear-quadratic model given by Equation 2, where for the latter model $x_i=D_i$, $y_i=\ln S_i/D_i$, $b_0=-\alpha$ and $b_1=-\beta$. The model given by Equations 1 and 3 were not used here because of the complexities of the calculation.

Table 1. Survival data for mammalian cells.[a]

Time of incubation at 37°C after first 5.05 Gy					
0.0 hr		2.5 hr		23.0 hr	
D	*S*	*D*	*S*	*D*	*S*
1.75	0.62	1.8	0.56	1.8	0.65
3.4	0.29	3.7	0.20	3.7	0.31
5.05	0.13	5.1	0.075	5.0	0.168
6.4	0.059	6.3	0.035	6.3	0.068
8.1	0.0168	7.6	0.014	7.8	0.033
9.7	0.0053	8.9	0.0050	9.0	0.013
11.4	0.0018			10.1	0.0052
13.0	0.00036				

[a] Data taken from Figure 11 of Elkind and Sutton (*1*). *D*, dose in Gy; *S*, survival.

Table 2. Estimated parameters of the hybrid scale model applied to the data in Table 1.

Incubation period, hr	Protective factor, ρ	Inactivation constant, b(Gy^{-1})	Correlation coefficient, r
0.0	2.0728	−0.7549	−0.9955
2.5	1.7396	−0.7938	−0.9916
23.0	2.4695	−0.7598	−0.9886

Results and Discussion

Figure 1 shows the results of fitting the proposed model to the data of the surviving fraction of mammalian cells irradiated with doses separated by three incubation periods of 0.0, 2.5, 23.0 hr. Figure 1*a–c* shows the given data points and the survival curves estimated by the proposed model. Each set of data points lies on each fitted curve of surviving fraction for its incubation period. This means that the proposed model is likely to be applicable to these data.

Figure 1*d* shows the linearity of all sets of surviving fraction on a semihybrid plot (a hybrid scale of surviving fraction, $H=\ln\rho S+\rho S$; see Table 2 for ρ), although these survival curves on a semilog plot have shoulders. The theory of hybrid scale (*5*) predicts that the survival curve on a semihybrid plot locates higher for strong protective systems than for weak protective systems, where the degree of protection of a system is defined by the protective factor ρ. Therefore, the lower location of survival curve for 2.5 hr suggests that it is less protective than that for 0 hr. The proximity of survival curves for 0 and 23 hr reflects that both give similar protective conditions, that is, the complete recovery of cells irradiated with 23-hr split-doses.

Table 2 gives estimated parameters of the proposed model to the data for each incubation period, including the correlation coefficients between $D/(1-S)$ and $\ln S/(1-S)$. All the absolute values of each of the correlation coefficients are close to 1 because of the goodness of fit of the proposed model to the data. The protective factor ρ for 2.5 hr is the smallest in all three cases because of degraded protective conditions. The inactivation constants b are similar among three cases. If the model given by Equation 4 is used, that is, $a \neq \ln\rho+\rho$, the protective factor is about 2 for 0 and 23 hr and about 1 for 2.5 hr; but the inactivation constants are not so different from those shown in Table 2. Thus the method of estimating parameters needs to be studied further.

The linear–quadratic model of the survival curve, applied to the data in the form given by Equation 8, gives $\alpha = 0.2551$, $\beta = 0.0281$, and $r = -0.9675$ for 0 hr; $\alpha = 0.2850$, $\beta = 0.0373$, and $r = -0.9300$ for 2.5 hr; and $\alpha = 0.1917$, $\beta = 0.0329$, $r = -0.9778$ for 23 hr, where r is the correlation coefficient. Therefore, the data did not fit the linear–quadratic model as well as the hybrid scale model.

The hybrid scale model can also be applied to the dose-response curve, which is concave upward on semilog paper, for low LET radiation. Then the response plotted in a logarithmic scale is linear against the given dose plotted in a hybrid scale. This application has been given in another papper (*6*).

Conclusion

The new concept of a hybrid scale model, extended from the hybrid lognormal distribution, was applied to data of shouldered survival curves. The hybrid scale model has two parameters: the protective factor ρ and the inactivation constant b. The model gave a good fit to the data of split-dose experiments with mammalian cells (*1*). The model also provides an explanation of the shoulder of survival curve and the effect of recovery time. This model is as simple as the linear–quadratic model of $S(D)=exp(-\alpha D-\beta D^2)$ but is applicable to the data both in the low- and the high-dose ranges. However, the method of estimating parameters needs to be studied further.

REFERENCES

1. Elkind, M. M., and Sutton, H. Radiation response of mammalian cells grown in culture. I. Repair of X-ray damage in surviving Chinese hamster cells. Radiat. Res. 13: 556–593 (1960).
2. UNSCEAR. Genetic and Somatic Effects of Ionizing Radiation, Annex B. Dose Response Relationships for Radiation-Induced Cancer. United Nations Scientific Committee on the Effects of Atomic Radiation, E.86.IX.9, United Nations, New York, 1986, pp. 183–191.
3. Hug, O., and Kellerer, A. M. Zur Interpretation der Dosiswirkungsbeziehungen in der Strahlenbiologie. Biophysik 1: 20–32 (1963).
4. Kumazawa, S., and Ohashi, Y. Hybrid lognormal distribution and its application [in Japanese]. Jpn. J. Appl. Stat. 15: 1–14 (1986).
5. Kumazawa, S. Dose distribution models of worker [in Japanese]. J. Atomic Energy Soc. Jpn. 29: 970–975 (1987).
6. Kumazawa, S. Some hybrid models applicable to dose-response relationships. Proc. International Conference on Radiation Effects and Protection, March 18–20, 1992, Mito, Japan, Japan Atomic Energy Research Institiute, Tokai, Japan, 1992, pp. 260–266.